REMARKS

Status Summary

Claims 1-27, 30-33, and 37-40 were canceled previously. Claims 28, 29, 34-36, and 41-59 are pending. Claims 42, 44-51, and 53-59 are withdrawn as being directed to a non-elected invention. Claims 28, 29, 34-36, 41, 43, and 52 are currently rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 28, 29, 34-36, 41, 43, and 52 are rejected under 35 U.S.C. §112, first paragraph, as allegedly non-enabling. Reconsideration in view of the following remarks and amendments is respectfully requested.

Request for Interview with the Examiner

Should the examiner be unpersuaded by the arguments presented herein, applicants respectfully request an in-person interview with the examiner to discuss the outstanding rejections.

Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 28, 29, 34-36, 41, 43, and 52 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite because the claims specify oligonucleotides that "correspond to" certain portions of SEQ ID NO:12. The examiner asserts that it would be unclear which sequences would correspond to SEQ ID NO:12 following deletion or mutation or one or more residues. Official action, page 2.

Applicants respond the claim language is made clear by Table 1 (page 120) of the specification as originally filed, which presents an alignment of the full-length and partial protox-1 amino acid sequences from *Arabidopsis*, maize, wheat, soybean, cotton, sugar beet, oilseed rape, rice, sorghum, and sugar cane. Although the sequences contain multiple substitutions and/or deletions when compared to each other, they are readily aligned using programs available in the art, for example, the PileUp program (GCG Package, available from the University of Wisconsin, Madison, WI). Additional protox-1 sequences could also be readily aligned. Accordingly, a skilled artisan recognizes from Table 1 those amino acid residues that

correspond to the designated positions in the soybean protox-1 sequence set forth as SEQ ID NO: 12.

Applicants further respond that the claims are consistent with related U.S. Patent 5,939,602 (the '602 patent), to which the instant application claims priority under 35 U.S.C. § 120. The '602 patent is presumed valid as provided by 35 U.S.C. § 282. Claim 1 of the '602 patent specifies a modified plant DNA molecule encoding a modified protox enzyme having at least one amino acid modification comprises an amino acid substitution "at a position corresponding to position 240, 245, 246, 388, 390, 451, 455, 500, or 536 of the comparative alignment shown in Table 1." Given that the language of pending claim 28 is substantially identical to the language of claim 1 of the '602 patent, which meets all statutory requirements for patentability, the claims are not indefinite.

Based upon the foregoing, applicants respectfully request the rejection be withdrawn.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 28, 29, 34-36, 41, 43 and 52 are rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement throughout the entire scope of the claims. Specifically, the examiner asserts that the instant application enables transforming the plastome of a tobacco plant with a mutation at position 226 of SEQ ID NO: 12, but fails to enable plastome transformation in any plant other than tobacco. Official action, pages 2-8. In support of this contention, the examiner cites Lutz et al., *Plant Physiology*, 2007, 145: 1201-1210 and Kanevski et al., *Plant Physiology*, 1999, 119: 133-141. The examiner relies on Lutz as teaching that, at the time of the instant invention, plastome transformation was routine only in tobacco. Official action, pages 7-8. The examiner relies on Kanevski et al., *Plant Physiology*, 1999, 119: 133-141 as teaching obstacles in plastome transformation. In particular, Kanevski discloses that plastome transformation of tobacco with a *Synechococcus* gene did not result in protein production, possibly due to incompatibility at the level of translation or an inability of the protein to assemble using the indigenous folding machinery. Official action, pages 7-8.

As a matter of Patent Office practice, the burden rests upon the Patent Office to establish a *prima facie* case of a failure to comply with 35 U.S.C. § 112, first paragraph, with respect to

the invention described and claimed in applicants' presumptively enabling patent application. *In re Marzocchi*, 58 C.C.P.A. 1069, 439 F.2d 220, 169 USPQ 367 (C.C.P.A. 1971).

The legal standard for enablement is whether one reasonably skilled in the art could make and use the invention based on the disclosure of the application and knowledge in the art without undue experimentation. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly excessive." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996).

Applicants maintain that the examiner has failed to make a *prima facie* case of lack of enablement in that, based on the disclosure of the instant application, a skilled artisan could readily transform plastomes of plants other than tobacco with nucleic acids encoding protox enzymes, as set forth in the claims, using routine techniques as described in the application and within the skill of one in the art.

The examiner's rationale for rejection is that, based upon the disclosures of Lutz and Kanevski, plastome transformation was not routine in the art as of the time of the instant invention. Applicants maintain their prior arguments that the examiner has overextended the interpretations of the cited references and/or taken selected passages from these references out of context. The examiner has stated that he is unpersuaded by applicants' prior comments, noting that the instant specification does not include a working example of a plant having a genetically modified plastome that expresses a modified protox enzyme other than tobacco. In further response to the rejection, applicants submit the following.

Initially, applicants point out that, at the time of the instant invention, plastome transformation techniques were available for use in plants other than tobacco. As one example, O'Neill et al., *Plant J.*, 1993, 3: 729-738 and Koop et al., *Planta*, 1996, 199: 193-201 describe

plastid transformation in *Physcomitrella patens*. As another example, PCT International Publication No. WO97/32977 describes plastid transformation in *Arabidopsis*. *See e.g.*, Example 2.

For still further examples, in applicant's prior response, it was noted that numerous patents describe relevant methods for plastome transformation, which patents are presumed valid under 35 U.S.C. § 282. In the present action, the examiner states that these patents are "inapposite to the patentability of the present claims" without offering any explanation as to why the patents are inapposite. *See* Official action, page 4. Applicants respond that these patents are relevant as demonstrating that plant plastid transformation of many species was within the level of skill in the art at the date of the instant invention. Specifically, U.S. Patent No. 5,451,513 includes claims directed to methods for obtaining stably plastid-transformed cells of a multicellular plant, which claims are not otherwise limited to any particular plant; U.S. Patent No. 5,545,817 claims methods for producing a peptide of interest in a solanaceous plant cell by plastid expression in the cell; U.S. Patent No. 5,545,818 claims methods for enhancing the expression of an insecticidal *Bacillus thuringiensis* toxin in a plant cell by plastid expression of the toxin in plants, including cotton; and U.S. Patent No. 5,576,198 claims methods of providing for transcription of a DNA sequence of interest in a plant plastid organelle using an expression construct, and further describes use of such methods in potato, corn, flowers such as petunia, rose, and carnation, fruits, such as tomato, and oilseed crops such as *Brassica*, soybean, corn, safflower, or sunflower. Using the claimed methods of the above-noted patents, one skilled in the art could readily accomplish plastid transformation in a variety of plants. The present invention provides an advance over these patents by introducing a modified DNA molecule that encodes a modified protox enzyme that confers resistance to an inhibitor of a naturally occurring protox enzyme, as set forth in the claims.

In response to the examiner's comments that the instant application does not include a working example of a plant having a genetically modified plastome that expresses a modified protox enzyme other than tobacco, applicants point out that working examples are not essential to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. Rather, all that is required is that the invention is disclosed in such manner that one skilled in the art will be able to practice the invention without undue experimentation. *In re Gould v. Quigg*, 822 F. 29 1074,

1078, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987); *In re Borkowski*, 422 F.2d 904, 164 USPQ 642 (CCPA 1970). *See also* MPEP 2164.02. Applicants further respond that this requirement has been met because later demonstrations of plastid transformation in additional plant species employ precisely the same steps as described in the instant application.

Specifically, the instant application teaches that plastome transformation may be achieved in a wide range of monocot and dicot species by (1) introducing a DNA molecule (in this case, a modified protox gene) into a plastome of a cell, wherein the DNA molecule is operatively linked to a promoter capable of inducing expression in both green and non-green chloroplasts, (2) expressing the encoded protein in the plastids of the plant cells and (3) selecting a cell comprising transformed plastomes. *See e.g.*, page 70, lines 15-20. With respect to (1), the application describes representative techniques for introducing the gene of interest into a cell, including ballistic particle acceleration. *See e.g.*, page 5, line 18, through page 6, line 11, and page 50, lines 3-21. The application further provides examples of promoters that may be used to express the DNA molecule, including native promoters of the DNA molecule of interest as well as heterologous promoters. *See e.g.*, pages 66-67, bridging paragraph, and page 55, line 26, through page 56, line 20. With respect to (2), the instant application describes plastome transformation vectors. *See e.g.*, page 68, lines 22-25. With respect to (3), the instant application describes selectable markers useful in the invention. *See* pages 70-71, bridging paragraph.

Example 43 of the instant application describes transformation of tobacco plastids using biolistic bombardment. Subsequent publications describing transformation of plastids also employed biolistic bombardment, including studies in cotton (Kumar et al., *Plant Mol. Biol.*, 2004, 56: 203-216), rice (Lee et al., *Mol. Cells*, 2006, 21: 401-410), soybean (Dufourmantel et al., *Plant Mol. Biol.*, 2004, 55: 479-489), cabbage (Liu et al., *Plant Cell Rep.*, 2007, 26: 1733-1744), lettuce (Kanamoto et al., *Transgenic Res.*, 2006, 15: 205-217; Ruhlman et al., *Plant Biotech. J.*, 2007, 5: 495-510), oilseed rape (Hou et al., *Transgenic Res.*, 2003, 12: 111-114), petunia (Zubko et al., *Transgenic Res.*, 2004, 13: 523-530), poplar (Okumura et al., *Transgenic Res.*, 2006, 15: 637-646), potato (Sidorov et al., *Plant J.*, 1999, 19: 209-216; Nguyen et al., *Plant Sci.*, 2005, 168: 1495-1500), and tomato (Ruf et al., *Nat. Biotechnol.*, 2001, 19: 870-875). Other studies used direct DNA uptake by protoplasts (*see e.g.*, Lelivelt et al., *Plant Mol. Biol.*, 2005,

58:763-774; Nugent et al., *Plant Sci.*, 2006, 170: 135-142), which the instant application identifies as an alternative technique for introduction of a DNA molecule into plastids. *See* page 50, lines 3-21.

Example 43 of the instant application also describes selection of transformants based upon spectinomycin resistance. Subsequent publications describing transformation of plastids also employed selection based upon spectinomycin resistance, including studies in carrot (Kumar et al., *Plant Physiol.*, 2004, 136: 2843-2854), rice (Lee et al., *Mol. Cells*, 2006, 21: 401-410), soybean (Dufourmantel et al., *Plant Mol. Biol.*, 2004, 55: 479-489), cabbage (Liu et al., *Plant Cell Rep.*, 2007, 26: 1733-1744), lettuce (Kanamoto et al., *Transgenic Res.*, 2006, 15: 205-217; Ruhlman et al., *Plant Biotech. J.*, 2007, 5: 495-510; Nugent et al., *Plant Sci.*, 2006, 170: 135-142), oilseed rape (Hou et al., *Transgenic Res.*, 2003, 12: 111-114), petunia (Zubko et al., *Transgenic Res.*, 2004, 13: 523-530), poplar (Okumura et al., *Transgenic Res.*, 2006, 15: 637-646), potato (Sidorov et al., *Plant J.*, 1999, 19: 209-216; Nguyen et al., *Plant Sci.*, 2005, 168: 1495-1500), tomato (Ruf et al., *Nat. Biotechnol.*, 2001, 19: 870-875), and cauliflower (Lelivelt et al., *Plant Mol. Biol.*, 2005, 58:763-774).

Examples 35-42 of the instant application describe preparation of various chimeric genes in tobacco plastid transformation vectors. Vectors designed for transformation of the tobacco plastid genome have also been used successfully for plastid transformation in other species, including potato and tomato. *See e.g.*, Sidorov et al., *Plant J.*, 1999, 19: 209-216; Ruf et al., *Nat. Biotechnol.*, 2001, 19: 870-875. In addition, based upon the disclosure of the present application and knowledge in the art at the time of the instant invention, one could readily prepare alternate plastid vectors. *See e.g.*, page 67, lines 22-29. *See also* O'Neill et al., *Plant J.*, 1993, 3: 729-738; Koop et al., *Planta*, 1996, 199: 193-201; and PCT International Publication No. WO97/32977.

Accordingly, publications of plastid transformation subsequent to the date of the instant invention, including those cited by Lutz, merely follow the steps set forth in the current specification. Therefore, the amount of experimentation needed to practice the full scope of the present claims is not undue.

As a final matter, Kanevski identifies difficulty in stability of the sunflower *rbcL* protein product in tobacco plants when expressed in tobacco plastids. Kanevski reports that tobacco

transformants containing the *rbcL* gene produced mRNA, however, the encoded protein was not detected. Applicants clarify that, without concern for the particular species of the DNA molecule being expressed, Kanevski does not address the question regarding the amount of experimentation required to transform plastomes in plants other than tobacco, as questioned by the examiner. The examiner acknowledges that the instant application enables plastome transformation in tobacco, and therefore, Kanevski does nothing to support the basis for rejection.

Based upon the foregoing, a *prima facie* case of lack of enablement has not been made and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a notice to that effect is earnestly solicited. If any points remain in issue, which may be best resolved through a personal or telephone interview, the examiner is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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